Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia

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Abstract

The effects of two different doses of magnesium sulphate (MgSO_4) were evaluated in a group of 15 full term infants with Apgar scores of <6 at 10 minutes, studied within 12 hours of delivery. Seven infants received 400 mg/kg MgSO_4 and eight received 250 mg/kg. After the larger dose, mean arterial pressure (MAP) fell by a mean of 6 mm Hg (13%) at one hour but was not significantly reduced thereafter. Respiratory depression lasted three to six hours. EEG readings and heart rate were not significantly different. Mean serum Mg^{2+} increased from 0.79 to 3.6 mmol/l at one hour. After 250 mg/kg MgSO_4 , MAP, EEG, tone and heart rate were unchanged. One infant developed transient respiratory depression. Mean serum Mg^{2+} rose from 0.71 to 2.42 mmol/l at one hour. MgSO_4 (400 mg/kg) has an unacceptable risk of hypotension; 250 mg/kg MgSO_4 was not associated with hypotension although respiratory depression can occur.

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Hypoxic-ischaemic encephalopathy following acute intrapartum asphyxia remains a significant cause of severe neurological disability. Among full term infants, about 1 in 1000 die or are severely disabled as a result of this condition.¹⁻⁴ Some children also survive asphyxia with minor or moderate learning difficulties, and these are potentially avoidable.^{5,6} No treatment for birth asphyxia or hypoxic-ischaemic encephalopathy has been shown to improve clinical outcome.⁴

An acute hypoxic-ischaemic insult initiates a cascade of biochemical events which lead, over the course of hours or even days, to irreversible neuronal injury. Neuronal injury is caused in part by excessive release and reduced uptake of glutamate.⁷ Glutamate mediates fast excitatory synaptic transmission and acts at specific receptor sites on cell bodies and post-synaptic dendrites. These receptors are classified according to specific ligands which bind them. It is thought that the N-methyl-D-aspartate (NMDA) receptor is particularly important in the development of post-asphyxial neuronal injury. High concentrations of glutamate cause the NMDA channels to open, allowing excessive amounts of calcium into the neurone, inducing irreversible cell injury. The immature brain may be particularly vulnerable to the

effects of excessive glutamate release as there is a far greater proportion of NMDA receptor sites in both the immature rat brain cortex and the developing human brain compared with the adult brain of the same species.⁸⁻¹⁰ Several drugs can antagonise the NMDA receptor. In particular, MK-801, when given after a hypoxic insult to the immature rat brain, affords impressive neuroprotection.¹¹ Unfortunately, MK-801 is potentially toxic and its use in human infants is not recommended.

Magnesium ions gate the NMDA channel in a voltage dependent manner by producing hyperpolarisation, and increasing the extracellular Mg^{2+} concentration may protect the brain from NMDA receptor mediated damage. The neuroprotective effect of Mg^{++} has been evaluated in a neonatal rat model and a single dose of 2 mmol/kg 15 minutes after an NMDA insult significantly reduces the severity of brain injury.¹² This effect was even greater when higher or multiple doses of magnesium sulphate were used. It has also been shown that a combination of magnesium sulphate (MgSO_4), methionine, and mannitol given 15 minutes after hypoxia-ischaemia in 8 day old rats, reduced the extent of neuropathological damage.¹³ MgSO_4 also seems to have a central anticonvulsant effect on hippocampal seizures¹⁴ and can cause cerebral vasodilatation.¹⁵

MgSO_4 has been widely used in obstetric practice for over 60 years.¹³ Its indications include suppression of preterm labour and management of pregnancy induced hypertension – Mg^{2+} has a vasodilator effect. Mg^{2+} readily transfers across the placenta. Lipsitz reported that maternal treatment with MgSO_4 led to a mean maternal serum Mg concentration of 2.5 mmol/l and mean cord serum Mg^{2+} of 2.4 mmol/l.¹⁶ Many of the infants showed flaccidity, hyporeflexia, and had a weak cry. Normally, cerebrospinal fluid Mg^{2+} is maintained about 30% higher than the serum concentration by an active pump.¹⁷ It has been calculated that an increase in extracellular Mg^{2+} of 0.5 to 1.0 mmol/l is enough to effect synaptic and neuronal activity.¹⁸ Hypermagnesaemia can affect the peripheral nervous system by releasing acetylcholine and reducing the responsiveness of the postsynaptic muscle membrane. Paralysis of voluntary muscles has been reported at plasma Mg^{2+} concentrations above 5 mmol/l.¹⁹

To plan a study evaluating the effectiveness of MgSO_4 as cerebral protection, it is important to perform a phase 1 study on (a) the pharmacokinetics of MgSO_4 in asphyxiated infants and (b) the effect of high dose intravenous MgSO_4 on physiological functions such as blood pressure, heart rate, respiration

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and neurological function. We planned a study to obtain this information, and a comparison of two different doses.

Methods

Infants were eligible for the study if:

- (a) gestation was equal to or greater than 35 weeks;
- (b) postnatal age was less than 12 hours;
- (c) major congenital malformations were absent;
- (d) 10 minute Apgar score was less than 6, or 5 minute Apgar score was less than 6, together with evidence of fetal distress defined as any of the following: sustained episodes of fetal bradycardia <100/minutes, thick meconium stained liquor, scalp pH of <7.11, or umbilical arterial pH of <7.00 or umbilical base deficit greater than -10 mmol/l;
- (e) the parent(s) gave informed consent to MgSO_4 administration.

One infant was included on the basis of respiratory arrest with profound hypoxaemia and acidosis at 5 hours of age. Five collaborating European neonatologists agreed at the start of the study to use two different dose regimens for MgSO_4 . In two centres 250 mg/kg MgSO_4 was given intravenously over 10 minutes. In three centres 400 mg/kg MgSO_4 was given intravenously over 10–30 minutes.

Before the infusion of MgSO_4 a continuous EEG (Oxford Medilog) or cerebral function monitor (CFM, Lectromed) recording was started. The following measurements were documented one hour before, immediately before, and one, three, six, 12, and 24 hours after the MgSO_4 infusion. Mean arterial pressure (MAP) was measured by a transducer attached to an umbilical or radial artery catheter in 13 cases and by oscillometry (Dinamap, Critikon) in two cases. Heart rate and respiratory rate were measured from chest electrodes. Muscle tone was documented using a modification of the Dubowitz neurological assessment.²⁰ Blood was taken for measurement of serum Mg^{2+} at 0, one, three, six, 12, and 24 hours in the routine clinical chemistry laboratories. The evaluation of MgSO_4 as a potential cerebral protective agent has been approved by the local research ethics committee in each participating centre.

Figure 1 Serum Mg^{++} concentrations (mean $\pm$ standard deviation) in seven infants receiving 400 mg/kg MgSO_4 and eight infants receiving 250 mg/kg MgSO_4 with birth asphyxia.

Figure 2 Mean arterial pressure (MAP) in each of the seven infants who received 400 mg/kg MgSO_4 .

Results

Seven infants received 400 mg/kg MgSO_4 and eight received 250 mg/kg MgSO_4 . Figure 1 shows the serum Mg^{2+} concentrations in the seven infants who received 400 mg/kg. The mean serum Mg^{2+} rose from 0.79 mmol/l to 3.6 mmol/l at one hour, 2.0 mmol/l at 12 hours, and remained increased at 1.6 mmol/l after 24 hours. MAP (fig 2) fell in the first hour by an average of 6 mm Hg (13%) ($P < 0.05$ by paired t test). The reduction in MAP was noted as soon as the MgSO_4 infusion had been given. In the most seriously ill infant, already requiring an infusion of 12 $\mu\text{g/kg/minute}$ dopamine to hold MAP over 40 mm Hg, 400 mg/kg MgSO_4 was associated with a decrease in the MAP from 48 to 33 mm Hg 30 minutes after the start of the MgSO_4 infusion; the dopamine infusion was immediately increased to 20 $\mu\text{g/kg/minute}$ (fig 3). At 45 minutes (five minutes after the MgSO_4 infusion had finished) MAP had fallen to 25 mm Hg but rose to 43 mm Hg at 60 minutes when the increased rate of dopamine infusion was maintained.

Mean heart rate fell by 10 beats a minute but this difference did not reach significance. All the infants receiving 400 mg/kg were intubated and mechanically ventilated before receiving the MgSO_4 and those that were breathing spontaneously ceased to breathe spontaneously for three to six hours. Two of the infants were profoundly hypotonic before the MgSO_4 infusion and there was no change in tone

Figure 3 Mean arterial pressure (MAP) in one infant who received 400 mg/kg MgSO_4 . The infant was already dependent on a dopamine infusion before the magnesium was started and the rate of dopamine infusion was increased because of the falling MAP. The nadir of MAP occurred five minutes after the magnesium infusion finished.

afterwards. The other five had varying degrees of tone which diminished for three to 12 hours after the MgSO_4 infusion. The EEG and CFM recordings before the magnesium infusion varied from extremely low background amplitude, or burst-suppression, to continuous normal amplitude activity but there was no change in amplitude or continuity after the MgSO_4 infusion.

The changes in serum Mg^{2+} after an infusion of 250 mg/kg are shown in fig 1. Serum Mg^{2+} rose from a mean of 0.71 mmol/l to 2.42 mmol/l at one hour, 1.52 mmol/l at 12 hours, and 1.12 mmol/l at 24 hours. There was no significant change in MAP (fig 4), heart rate, tone, or EEG. Four out of eight infants were already intubated and ventilated before the MgSO_4 infusion. One of the infants who was not intubated became transiently desaturated (oxygen saturation by pulse oximeter was 60–70%) with shallow respiration after receiving 250 mg/kg and required five minutes of oxygen by face mask and bag to restore normal saturation. This infant did not require intubation and breathed satisfactorily later. The other three infants who were not intubated breathed satisfactorily throughout.

Using standard pharmacokinetic methods,²¹ semilogarithmic plots of serum concentration *v* time indicate that the elimination of Mg^{2+} displays biphasic kinetics. The population mean half lives of the terminal elimination phases ($t_{1/2\beta}$) were 28.06 hours and 27.61 hours, respectively, for the low and high dose regimens.

Two infants had lumbar punctures as part of standard procedure and cerebral spinal fluid Mg^{2+} was 1.43 mmol/l about three hours after MgSO_4 infusion (*v* 2.15 in serum) and 1.71 mmol/l about 10.5 hours after the infusion (*v* 1.91 mmol/l in serum).

Discussion

The vasodilator properties of magnesium sulphate have been used extensively for the treatment of pre-eclampsia¹⁴ and, to a limited extent, persistent pulmonary hypertension in the newborn.²² The drop in blood pressure (mean 6 mm Hg or 13% at one hour) noted with the higher dose can be explained on this basis. The drop in MAP from 48 to 25 mm Hg in one infant, necessitating an immediate increase in the dopamine infusion rate, indicates that hypotension after high dose

Mg^{2+} could have serious consequences if monitoring is not good and immediate corrective action is not taken. There was no significant reduction in MAP (compared with the pretreatment level) at three hours or later. There was no significant drop in MAP at one hour in the infants receiving 250 mg/kg MgSO_4 .

The neuromuscular blocking effect of Mg^{2+} was noted in the infants receiving 400 mg/kg where spontaneous respiration was abolished for several hours and muscle tone was decreased. The lack of change in the EEG is evidence that hypotonia does not have a central role. Although muscle tone did not show an objective decrease in the infants receiving 250 mg/kg, the transient respiratory depression in one unintubated infant was most likely the result of partial neuromuscular blockade.

On the basis of limited data, cerebrospinal Mg^{2+} concentrations were lower than those in serum and the cerebrospinal fluid:serum ratio was lower with earlier rather than later sampling. This apparent delay in Mg^{2+} transfer could be explained by limited capacity of the active pump across the blood-brain barrier. The turnover of the cerebrospinal fluid reservoir might also be slow enough to prevent a rapid rise in Mg^{2+} . Clearly any cerebral protective effect of Mg^{2+} is dependent on its penetrating the brain rapidly.

We conclude that the use of 400 mg/kg MgSO_4 in asphyxiated infants is associated with an unacceptable risk of hypotension. Hypotension after asphyxia would be particularly hazardous in situations with poor staffing or inadequate monitoring equipment. The lower dose of MgSO_4 (250 mg/kg) was not associated with hypotension but may cause respiratory depression. Thus we recommend that respiration should be carefully assessed and monitored in infants before this dose is given. If there is any doubt about the adequacy of spontaneous respiration, intubation and ventilation before the first dose of MgSO_4 would be advisable. As the blood pressure response to MgSO_4 varied considerably among infants, continuous or frequent blood pressure measurement is necessary as well as the availability of dopamine. Secondary injury to the posthypoxic neonatal brain can occur over a period that may last as long as 72 hours.²³ If Mg^{2+} were to be evaluated as a neuroprotective agent in severely asphyxiated infants a dosing regimen aimed at maintaining increased concentrations for 72 hours would be necessary. Based on the estimates of a plasma half life of MgSO_4 reported here, an effective dosing regimen comprises a loading dose of 250 mg/kg, followed by two further infusions of 125 mg/kg at 24 hours and 48 hours. This would ensure that plasma concentrations of Mg^{2+} were maintained in the range 1.2 to 2.5 mmol/l.²⁴

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Figure 4 Mean arterial pressure in eight infants receiving 250 mg/kg MgSO_4 .

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